Fermented dairy foods rich in probiotics and cardiometabolic risk factors: a narrative review from prospective cohort studies

Judit Companys[1,2], Anna Pedret*[1,2], Rosa M Valls[2,1], Rosa Solà*[2,1,3], Vicente Pascual[4]

[1]Eurecat, Centre Tecnològic de Catalunya, Unitat de Nutrició i Salut, Reus, Spain.

[2]Universitat Rovira i Virgili, Facultat de Medicina i Ciències de la Salut, Functional Nutrition, Oxidation and Cardiovascular Disease Group (NFOC-SALUT), Reus, Spain.

[3]Hospital Universitari Sant Joan de Reus, Reus, Spain.

[4]Centro de Salud Palleter. Universidad CEU-Cardenal Herrera. Castellón

***Corresponding author**

Dra. Anna PEDRET

Eurecat, Centre Tecnològic de Catalunya,

Unitat de Nutrició i Salut.

Av. de la Universitat, 1,

43204 Reus, Spain

Tel: (+34) 977 75 14 84

E-mail: anna.pedret@eurecat.org

and

Dra. Rosa SOLÀ

Universitat Rovira i Virgili, Facultat de Medicina i Ciències de la Salut, Functional Nutrition, Oxidation and Cardiovascular Disease Group (NFOC-SALUT), Reus, Spain.

Hospital Universitari Sant Joan de Reus, Reus, Spain.

43201 Reus, Spain

Tel: (+34) 977 75 93 69

E-mail: rosa.sola@urv.cat

Word count: 5603 words.

Abstract

Probiotic foods, including fermented dairy (FD) products such as yogurt and cheese, naturally contain live microorganisms, but the relationship between the consumption of probiotic foods and health is unclear. The aim of the present narrative review is to integrate the available information on the relationship between the most studied FD products, which are yogurt and cheese, and cardiometabolic risk factors obtained from meta-analysis, systematic reviews of prospective cohort studies (PCSs) and PCSs published up to 2 November 2019. Additionally, the effects identified by randomized controlled trials of less-studied FD products, such as kefir and kimchi, on cardiometabolic risk factors are provided. PCSs have shown that the consumption of cheese, despite its high saturated fat content, is not associated with expected hypercholesterolemia and an increased cardiovascular risk. PCSs have revealed that the total consumption of FD appears to be associated with a lower risk of developing stroke and cardiovascular disease. The consumption of yogurt seems to be associated with a lower risk of developing type 2 diabetes. There is a lack of sufficient evidence of a protective relationship between FD or cheese consumption and metabolic syndrome. Moreover, the association of FD, cheese and yogurt with hypertension needs further evidence.

In conclusion, the intake of fermented foods containing probiotics, particularly yogurt and cheese (of an undetermined type), opens up new opportunities for the management of cardiometabolic risk factors.

Keywords: *probiotics, fermented dairy products, type 2 diabetes, cardiovascular disease*

Introduction

Probiotics are live microorganisms that, when administered at an adequate quantity, can modulate the gut microbiome and confer health benefits to the host (Parvez et al. 2006; Toscano et al. 2017). The usual routes for the administration of probiotics are a in powder or capsule or inclusion in a dairy product or other food matrix (Toscano et al. 2017); however, probiotics are also present in natural form as a result of fermentation, as in the case of dairy foods (Gille et al. 2018).

Fermented foods contain one or more probiotics; these are dominated by lactic acid bacteria, including *Lactobacillus*, but the fermentation process also includes other bacteria and yeasts (Gille et al. 2018).

However, the presence of bacteria and yeast does not always result in a probiotic food or beverage; for example, the yeast in bread is heat-inactivated, and the bacteria in wine and beer are removed by filtration (Rezac et al. 2018).

Thus, to consider a food or beverage probiotic, the bacteria must be resistant to gastric acid, bile salts and enzymes and be able to bind to the epithelium of the small intestine in sufficient quantity (more than 10^6-10^7 colony-forming units (CFUs)/mL at the time of consumption) to exert probiotic activity (Ranadheera et al. 2017).

A source for the generation of probiotics is the food fermentation process, which focuses on improving the organoleptic qualities of the food, decreasing spoilage, increasing the available consumption time and modifying nutritional properties (Xiang et al. 2019); however, the available information on fermentation as a source of probiotic food and its relationship with cardiovascular disease (CVD) risk factors is inconclusive (Xiang et al. 2019). The potential inherent benefits associated with the intake of fermented foods might be due to their probiotic activity and/or biogenic elements in the host. Biogenic elements are aspects of live organisms and are necessary for the development of the probiotic itself. The basic biogenic compounds are carbon, hydrogen, oxygen and nitrogen, as well as other molecules and constituents acquired during the fermentation process (Gille et al. 2018; Rezac et al. 2018).

Fermented foods are good vehicles for supplying probiotics to the digestive system and can modify and improve the composition of gut microbiota, in which *Bacteroidetes* and *Firmicutes* are predominant (>90% of the total intestinal microbial population) (Marco et al. 2017). Information regarding the role of the gut microbiota in association with risk factors for cardiometabolic diseases, such as diabetes and CVD, which result in high morbidity and mortality throughout the world (Muñoz-Garach et al. 2016; W.H. Wilson Tang et al. 2017), is scarce. The known cardiometabolic risk factors include obesity, high serum concentrations of low-density lipoprotein cholesterol (LDL-C), high serum triglyceride levels, reduced serum concentrations of high-density lipoprotein cholesterol (HDL-C), hypertension and insulin resistance (Companys et al. 2020; Guo et al. 2017; Tapsell 2015; Thushara et al. 2016). The population impact of cardiometabolic factors was estimated to equal 38% in 2018, and this percentage increased to more than 60% in certain individuals, particularly women older than 65 years of age (Statista 2018). Among cardiometabolic risk factors, the gut microbiota can present dysbiosis or alteration of the normal quantitative and/or qualitative balance, which is characterized by an imbalance in the *Firmicutes*/*Bacteroidetes* ratio (a reduction in the abundance of *Firmicutes* and an increase in the abundance of *Bacteroidetes)* (Han and Lin 2014). Dysbiosis can be modified through the oral administration of probiotics, as has been demonstrated in RCTs (Borgeraas et al. 2018; Firouzi et al. 2013; Seganfredo et al. 2017; Yoo and Kim 2016). Thus, the use of foods rich in probiotics to affect the gut microbiota balance might be a strategy for the prevention or attenuation of cardiometabolic complications (Companys et al., submitted; Tapsell, 2015; Thushara et al., 2016; Rondanelli et al., 2017).

Based on the abovementioned results, the aim of the present narrative review is to integrate the information available from prospective cohort studies (PCSs) on the relationship between the regular consumption (daily/weekly) of the most frequently studied fermented dairy (FD) foods that provide probiotics, such as yogurt and cheese, and cardiometabolic risk factors. In addition, the effects of less-studied FD products, such as kefir and kimchi, on cardiometabolic risk factors, as observed in randomized controlled trials (but not PCSs due to a lack of previous studies on this subject), are described.

Literature search

The literature search used in the present narrative review was based on the general principles published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). The PRISMA flowchart (**Supplementary Figure 1**) and checklist (**Supplementary Table 1**) were utilized.

Search strategy

The bibliographic review for the present narrative review was performed in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The following MeSH terms were used for the literature search named of fermented foods, such as a “fermented dairy”, “cheese”, and “yogurt”, in combination with “cardiovascular disease” and “cardiovascular risk factors” using the connector “AND”. Articles were selected if they described meta-analyses, systematic reviews or PCSs that assessed the relationship between FD intake and CVD. The search included studies published up to 2 November 2019.

Data collection and extraction

Table 1. Levels of evidence for the association between fermented dairy product consumption and cardiometabolic risk factors based on the present narrative review of the results from meta-analyses, systematic reviews of PCSs and PCSs. The level of risk (low, uncertain or neutral) in the reported relationships between total FD, cheese and yogurt consumption and cardiometabolic risk factors is provided.

Selection of included studies

The authors identified 251 articles from the PubMed database and included six articles obtained from a review of the references of the retrieved articles. After removing duplicate articles, the authors screened the titles and abstracts of 184 articles, and ultimately, a total of 21 articles were included in the present narrative review.

Total FD, cardiometabolic risk factors and mortality in PCSs

FD foods, including yogurt and cheese, are heavily consumed by the general population (Guo et al. 2017). Recommendations for dairy intake make no distinction between the consumption of fermented or unfermented foods and note the importance of eating at least three servings of dairy foods (e.g., milk, yogurt, cheese, and kefir) per day due to their important nutritional role in calcium metabolism and their high levels of protein with high biological quality, independent of their probiotic contents and their potential cardiometabolic benefits (Britten et al. 2012).

Some PCSs did not distinguish, between the types of FD products consumed, and thus, all of those studies were included in the "fermented dairy" category. For this reason, the authors have included the available information for all FD products. The information obtained from the meta-analyses, systematic reviews of PCSs and PCSs evaluating the relationship between cardiometabolic risk factors and the consumption of all FD products is presented in **Table 1**.

Total mortality risk and consumption of FD. A meta-analysis that included 29 PCSs with 938,465 participants and a follow-up between 5 and 15 years revealed an inverse association between the total consumption of all FD products and all-cause mortality, an increased FD consumption was associated with a 2% in decreased in risk (RR 0.98, 95% CI: 0.97 to 0.99, I^2 = 94.4%) (Guo et al. 2017).

CVD and stroke risk and consumption of FD. A meta-analysis of 29 PCSs with 938,465 participants and 28,419 patients with coronary heart disease (CHD) found an inverse association between the total consumption of FD products, including sour milk, cheese or yogurt, and the risk of CVD [an increase in consumption of 20 g/d was associated with a 2% reduction in risk, (RR 0.98, 95% CI: 0.97 to 0.99, I^2 = 87.5%)] (Guo et al. 2017). Additionally, a meta-analysis of 15 PCSs that included 28,138 stroke events and 764,635 participants aged 30 to 103 years was also included (Hu et al. 2014). This study revealed that the total consumption of fermented milk products resulted in a significant risk reduction of 20% (RR 0.80, 95% CI: 0.71 to 0.89, I^2 = 0.00%) and that cheese consumption was associated with a significant reduction in stroke risk of 6% (RR 0.94, 95% CI: 0.89 to 0.99, I^2 = 0.00%) (Hu et al. 2014).

However, another PCS that included the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort, which comprised 34,409 Dutch men and women aged 20-70 years who were free of CVD or cancer at baseline (Praagman et al. 2015), did not provide consistent evidence regarding an association of total FD consumption with a decrease in total mortality, and none of the subtypes of fermented foods showed significant benefits in terms of total or cardiovascular mortality (Praagman et al. 2015).

Consistent with the abovementioned results of systematic reviews and meta-analyses, a systematic review of PCSs that investigated the association of total dairy consumption with CVD, coronary artery disease (CAD), stroke, hypertension, metabolic syndrome (MetS), and type 2 diabetes mellitus (T2D) concluded that the consumption of various forms of FD products had either a favorable or neutral relationship with cardiovascular-related clinical outcomes, but this conclusion was based on limited and uncertain evidence (Drouin-Chartier et al. 2016).

MetS risk and FD consumption. A meta-analysis of 11 PCSs examined the association of the consumption of dairy products and/or different subtypes of dairy with the risk of MetS, and the comparison of the highest and lowest categories revealed that total yogurt consumption was associated with a 26% decrease in the risk of MetS (RR 0.74, 95% CI: 0.66 to 0.82, I^2 = 0.00%) (Mena-Sánchez et al. 2018). Thus, PCSs have revealed that the consumption of all types of low-fat dairy products, milk, and yogurt is inversely associated with the risk of MetS (Mena-Sánchez et al. 2018).

Hypertension risk and FD consumption. A systematic review of 9 PCSs found that, only 4 studies reported data on FD intake. Based on a sample size of 7,641 volunteers and 2,475 hypertension cases and a follow-up time of 2 to 15 years, the consumption of total FD (range intake ≈ 84-201 g/d) was not statistically associated with the development of hypertension (Soedamah-Muthu et al. 2012). The pooled relative hypertension risks per 150 g/d increase in consumption were [RR 0.99, 95% CI: 0.94 to 1.04, I^2 = no data available (NDA)] for total FD (Soedamah-Muthu et al. 2012).

Summary of PCS findings on total FD intake and cardiometabolic risk factors

Total FD intake is associated with low risks of CVD and stroke, as demonstrated by different systematic reviews and meta-analyses of PCSs. Moreover, as demonstrated in some studies, FD consumption is associated with MetS. However, the limited data available from PCSs cannot confirm any beneficial relationship of total FD with MetS **(Table 1)**.

Cheese, cardiometabolic risk factors and mortality in PCSs

The dietary matrix of cheese involves a complex nutritional composition, which is characterized by its composition of not only saturated fats (Ros et al. 2015) but also other nutrients present in fermented cheese, such as probiotics, which can exert a protective effect on CVD (Marco et al. 2017). Moreover, cheese is an excellent source of calcium and vitamin

D. Additionally, in fermented cheeses, andrastin A and the roquefortine exhibit hypocholesterolemic capacity by inhibiting the farnesyl transferase enzyme, which consequently inhibits cholesterol synthesis in the liver (Ros et al. 2015). The andrastin A contents of some Spanish fermented cheeses, such as Cabrales, Valdeón and Bejes-Tresviso, are similar to those found in other fermented Danish and French cheeses (Fernández-Bodega et al. 2009), which could contribute to reduced cholesterol production. Whether the greater consumption of cheese, which is rich in saturated fat, by the French population is responsible for the so-called French paradox, which is defined by low cardiovascular morbidity and mortality despite a high intake of saturated fat, is unclear (Petyaev and Bashmakov 2012). The consumption of cured cheese has traditionally been associated with deleterious effects on the lipid profile; however, the hypercholesterolemic effect of saturated fatty acids is attenuated when these are provided through a food matrix such as cheese (Nagpal et al. 2011). As a result, recent results from the European EPIC cohort (European Prospective Investigation Into Cancer and Nutrition) of 409,885 men and women in nine European countries measured lipids in a subsample during a mean follow-up of 12.6 years and found that the consumption of cheese was inversely associated with serum non-high-density lipoprotein cholesterol levels (Key et al. 2019).

CVD risk and cheese consumption. Four meta-analyses of PCSs evaluated cheese consumption and the risk of all-cause mortality, CHD or CVD (Alexander et al. 2016; Chen et al. 2017; de Goede et al. 2016; Guo et al. 2017). One of these studies performed additional individual analyses of cheese and found a 2% decrease in cardiovascular risk (RR 0.98, 95% CI: 0.95 to 1.00, $I^2 = 82.6\%$) per 10-g increase in the daily intake of cheese (Guo et al. 2017). Additionally, a meta-analysis of PCSs revealed that cheese consumption (50 g/d) was inversely associated with CHD (RR 0.90, 95% CI: 0.84 to 0.95, $I^2 = 0.00\%$) (Chen et al. 2017). Moreover, a meta-analysis of 31 PCSs found that cheese intake was inversely and not significantly associated with CHD (RR 0.82, 95% CI: 0.72 to 0.93, $I^2 = 0.0\%$) and stroke (RR 0.87, 95% CI: 0.77 to 0.99, $I^2 = 33.5\%$) (Alexander et al. 2016). Furthermore, a systematic review and meta-analysis of 18 PCSs revealed that an increase in cheese consumption of 40 g/d was inversely associated with a nonsignificant 3% lower risk of stroke (RR 0.97, 95% CI: 0.94 to 1.01, $I^2 = 31.2\%$) (de Goede et al. 2016). In contrast, a meta-analyses of 18 PCSs compared the highest and lowest rates of cheese consumption and found that the highest consumption was associated with a 6% reduction in stroke risk (RR 0.93, 95% CI: 0.88 to 0.98, $I^2 = 86\%$) (Hu et al. 2014). Only one PCS with 24,474 participants compared the highest quartile of consumption (224 g/d) with the lowest quartile (56 g/d), and it revealed that the highest quartile was associated with lower total mortality (HR 0.92, 95% Cl: 0.87 to 0.94, I^2 = NDA) (Mazidi et al. 2018).

HDL-C levels,* MetS *risk and cheese consumption. The PCSs provided scarce information on the association between HDL-C levels and MetS but found a cross-sectional association between high cheese intake and higher HDL-C levels ($P_{trend} = 0.002$) (Sonestedt et al. 2011).

T2D risk and cheese consumption. In two PCSs, cheese consumption was inversely related to the risk of developing T2D (Sluijs et al. 2012), and a higher consumption of cheese (higher than 55.7 g/d) was associated with a significant reduction of 70% in the risk of developing T2D compared with the reduction associated with lower consumption (less than 32 g/d) (HR 0.30, 95% CI: 0.10 to 0.92, I^2 = NDA) (Hruby et al. 2017). Similarly, an umbrella review of PCSs (Godos et al. 2019) and a PCS of 108,065 Swedish men and women (Johansson et al. 2019) revealed that a greater intake of cheese tended to be associated with a lower risk of developing T2D in both men and women (HR 0.79, 95% CI: 0.68 to 0.92, I^2 = NDA).

MetS *and cheese consumption.* In a PCS of 1,868 men and women (aged 55-80 years) without MetS at baseline that formed part of the PREDIMED study, a median follow-up of 3.2 years (Babio et al. 2015) revealed a higher MetS incidence among subjects with a high intake of cheese (HR 1.31, 95% CI: 1.10 to 1.56, I^2 = NDA). Another PCS analyzed the association between cheese consumption based on continuous variables and the risk of MetS using data from the Epidemiological Study on Insulin Resistance Syndrome (DESIR) study, which included 3,435 men and women who completed a food frequency questionnaire at baseline and after 3 years; the results showed that a lower risk of MetS development (RR 0.82, 95% CI: 0.71 to 0.95, I^2 = NDA) was associated with a one-category increase in cheese consumption (Fumeron et al. 2011). Moreover, higher cheese intake and calcium density were associated with a lower increase in waist circumference and lower triglyceride levels. The Calcium density was also found to be associated with a decrease in hypertension and a lower 9-year increase in plasma triglyceride levels. Thus, a higher consumption of dairy products and calcium was associated with a lower 9-year incidence of T2D (Fumeron et al. 2011). A meta-analysis comparing the highest and lowest categories was not performed (Mena-Sánchez et al. 2018) because only one study was available for the analysis (Babio et al. 2015).

Summary of the findings of PCSs examining cheese intake and cardiometabolic risk factors

Based on all the mentioned studies, the consumption of cheese, regardless of its fat content, is associated with decreases in cardiovascular and stroke risks. Surprisingly, cheese intake had a beneficial association with the risk of developing T2D. However, there is limited evidence to support the presence of a protective relationship between cheese consumption and MetS, and the association of cheese consumption with hypertension remains uncertain (Soedamah-Muthu et al. 2012) **(Table 1).** However, dietary recommendations regarding the consumption of cured cheeses, which have high sodium contents, are limited in cases of hypertension (Pérez-Jiménez et al. 2018).

Yogurt, cardiometabolic risk factors and mortality in PCSs

Yogurt is a semisolid product of fermented milk that has been consumed for centuries and is an important dietary source of nutrients such as calcium (Fernandez and Marette 2017). Yogurt consumption is related to a healthy lifestyle (Tremblay and Panahi 2017). In particular, yogurt is the most frequently evaluated FD product in observational studies (Drouin-Chartier et al. 2016), which suggest the presence of a protective relationship between yogurt consumption and CVD (Astrup 2014).

All-cause mortality risk and yogurt consumption. A meta-analysis of 29 PCSs revealed that yogurt consumption was not associated with all-cause mortality (RR 0.97, 95% CI: 0.85 to 1.11, I^2 = 65.8%) (Guo et al. 2017).

CVD, CHD and stroke risk and yogurt consumption. The evidence generated by systematic reviews and meta-analyses of PCSs of moderate quality showed a neutral association between the consumption of yogurt and the risk of CVD, stroke or CHD (Alexander et al. 2016; de Goede et al. 2016; Guo et al. 2017). Moreover, a meta-analysis of 9 PCSs involving a total of 291,236 participants showed that the consumption of $\geq$200 g/d of yogurt was significantly associated with a lower risk of CVD compared with the consumption of <200 g/day (Wu and Sun 2017). In contrast, a systematic review of 22 PCSs with 579,832 participants evaluated reductions in CVD risk but found nonsignificant results (Soedamah-Muthu and de Goede 2018). Consistent with these results, a PCS with 24,474 participants, revealed that yogurt consumption significantly reduced total CAD and stroke mortality (HR 0.88, 95% CI: 0.84 to 0.92, I^2 = NDA) (Mazidi et al. 2018). Recently, in the Prospective Urban Rural Epidemiology (PURE) study, a large multinational PCS of individuals aged 35-70 years in 21 countries on five continents, the dietary dairy intakes of 136,384 individuals were recorded using validated, country-specific validated food frequency questionnaires. Between between January 1, 2003, and July 14, 2018, 10,567 composite events (deaths [n=6796] or major cardiovascular events [n=5855]) were recorded during the 9.1 years of follow-up. This PCS showed that a higher intake of yogurt (>1 serving vs no intake) (RR 0.86, 95% CI 0.75 to 0.99; I^2 = NDA) was associated with a lower risk of the composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, stroke, or heart failure) (Dehghan et al. 2018).

Hypertension risk and yogurt consumption. A systematic review of 9 PCSs, which included a sample size of 57,256 participants, 15,367 incident hypertension cases, and a follow-up time between 2 and 15 years, found no association between yogurt intake (10 to 79 g/d) and the incidence of hypertension (Soedamah-Muthu et al. 2012). In contrast, two Nurses' Health Study (NHS) cohorts (n=69,298), the NHS II (n=84,368) and the Health Professionals Follow-Up Study (HPFS, n=30,512) revealed that the consumption of at least five servings of yogurt per week (vs. <1 serving per month) was associated with lower risks of hypertension (HR 0.81, 95% CI: 0.75 to 0.87, I^2 = NDA, HR 0.83, 95% CI: 0.77 to 0.90, I^2 = NDA, and HR 0.94, 95% CI: 0.83 to 1.07, I^2 = NDA, respectively) (Buendia et al. 2018). Moreover, the same study revealed that the consumption of at least five servings of yogurt per week resulted in a 19% lower risk of hypertension (RR 0.81, 95% CI: 0.75 to 0.87, I^2 = NDA) (Buendia et al. 2018).

MetS *risk and yogurt consumption.* A meta-analysis of 4 PCSs compared the highest and lowest categories of yogurt consumption and found that the highest category was inversely associated with the risk of MetS (RR 0.74, 95% CI: 0.66 to 0.82, I^2 = 0.00%) (Mena-Sánchez et al. 2018).

T2D risk and yogurt consumption. The results of a meta-analysis of 17 PCSs, with 426,055 participants found that higher consumption of yogurt was associated with a nonsignificantly lower risk of T2D compared with a lower consumption of yogurt (RR 0.78, 95% CI: 0.60 to 1.02; $I^2 = 70\%$) (Aune et al. 2013). The reduction in the risk of T2D observed in meta-analyses of PCSs varied between 14% with a yogurt intake of 80 g/d compared with no yogurt intake (Gijsbers et al. 2016) and 22% with a yogurt intake of 200 g/d (Aune et al. 2013).

The relationship between the potential protective role of yogurt consumption and the prevention of T2D was corroborated in a recent review of 13 PCSs, which described an inverse association between the frequency of yogurt consumption and the risk of developing T2D (Salas-Salvadó et al. 2017).

Summary of the findings of PCSs on yogurt intake and cardiometabolic risk factors.

The authors have updated the results from different meta-analyses and systematic reviews of PCSs examining the relationship between yogurt consumption and risk factors for cardiometabolic disease and mortality, and these data indicate that yogurt consumption can reduce T2D risk. Further RCTs are needed to investigate the interesting negative association between yogurt consumption and T2D obtained in PCSs (Panahi et al. 2017). In addition, more evidence is needed to confirm the relationship between yogurt consumption and reductions in hypertension and MetS, and the association between yogurt consumption and reduced risks of CVD and stroke are not supported by sufficient evidence **(Table 1).**

Kefir, cardiometabolic risk factors and mortality

As mentioned above, PCSs have not reported an association between kefir and CVD mortality or/and CVD risk factors. Kefir is a fermented milk product that originated in the Caucasus and is produced by lacto-alcoholic fermentation induced by bacteria (e.g., *Lactobacillus acidophilus*, *Lactobacillus kefiranofaciens*, and *Lactobacillus plantarum*) and yeasts (e.g., *Kluyveromyces marxianus* and Candida kefir). As a result, the fermented kefir produces minimal amounts of lactic acid and alcohol (usually not exceeding 2%) (Rosa et al. 2017).

The high levels of probiotics in kefir can regulate the gut microbiota and exert an anti-inflammatory effect mediated by their action on certain cytokines (Carasi et al. 2015; Kim et al. 2019). In addition, *Lactobacillus plantarum*, which is present in kefir, exhibits an antioxidant effects by synthesizing enzymes such as peroxidase and superoxide dismutase, among others (Wei Tang et al. 2018).

Limited evidence of the hypocholesterolemic effect of kefir in experimental animal models has been observed (Huang et al. 2013), and this effect has not been described in humans. The hypocholesterolemic effect of kefir could occur because its high levels of probiotics inhibit cholesterol absorption in the small intestine, as demonstrated in different animal models and bacterial cells (Pimenta et al. 2018). Additionally, to explain the effect of kefir on cholesterol reduction, another mechanism has also been proposed due to the presence of a specific yeast strain that exerts hydrolase action in bile salts; this mechanism involves the deconjugation of bile acids and their elimination via feces. The resulting increase in the demand for cholesterol for the synthesis of bile salts induces a hypocholesterolemic effect (Pimenta et al. 2018).

Similarly, in a spontaneously hypertensive animal model, kefir consumption exerted an antihypertensive effect that appears to be mediated by two mechanisms: a) inhibition of the angiotensin-converting enzyme and b) the effect of probiotics in preventing or reversing dysbiotic bowel, which results in proinflammatory and pro-oxidant phenomena (Pimenta et al. 2018).

Other probiotic foods and cardiometabolic risk factors

Few results regarding other food sources of probiotics, such as kimchi and fermented soybeans, have been reported due the small number of RCTs that have been conducted; as a result, no clear conclusions can be drawn.

Kimchi is a traditional Korean food that consists of a blend of fermented vegetables, such as Chinese cabbage, turnips and others. The effects of kimchi on cardiometabolic factors have been evaluated in a few RCTs (An et al. 2013; Eun Kyoung Kim et al. 2011). One study investigated 21 participants with prediabetes who consumed either fresh (1-day-old) or fermented (10-day-old) kimchi, and after 4-week washout period, the participants switched to the other type of kimchi and consumed the new type for the next 8 weeks (An et al. 2013). The results revealed that kimchi had beneficial effects on factors related to glucose metabolism, such as reductions in glycosylated hemoglobin, homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin, and anthropometric factors, such as reductions in body weight, body mass index and waist circumference, in participants with prediabetes (An et al. 2013). In addition, fermented kimchi exerts additional effects for reducing hypertension and resistance/insulin sensitivity in prediabetic participants (An et al. 2013). Similarly, another RCT examined the effects of kimchi consumption by 22 overweight and obese patients with a body mass index ≥25 kg/m^2 who were randomly assigned to two 4-week diet phases separated by a 2-week washout period. During each diet phase, the subjects consumed either fresh or fermented kimchi for 4 weeks. In these overweight or obese patients, fermented kimchi consumption significantly decreased hypertension and insulin resistance and improved glucose tolerance compared with the consumption of fresh kimchi (Eun Kyoung Kim et al. 2011). Moreover, fermented kimchi consumption for 4 weeks resulted in significant decreases in abdominal obesity, basal glycemia, total cholesterol, and hypertension compared with the consumption of fresh kimchi (Eun Kyoung Kim et al. 2011).

However, our literature review did not identify any PCSs examining the relationship between kimchi consumption and cardiometabolic risk factors. In relation to the consumption of fermented soy products, a PCS of a Japanese cohort of 926 men and 3,239 women aged 40 to 69 years with normotension showed an inverse association between the intake of fermented soy products and the development of hypertension but no association between the consumption of unfermented soy foods and hypertension (Nozue et al. 2017). A possible mechanism of action is the rich concentration of bioactive peptides that were generated during the fermentation of soy, which can mediate a vasodilator effect on the vascular wall and inhibit the angiotensin-converting enzyme (Wang et al. 2017).

Additionally, further research is urgently needed to compare the impact of low-fat dairy with that of regular-and high-fat dairy on cardiovascular-related clinical outcomes and to harmonize the findings with the current recommendations to consume low-fat dairy (Carson et al. 2019). For example, the most recent dietary recommendations for reducing human blood cholesterol emphasize the consumption of fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean protein sources, nuts, seeds, and liquid vegetable oils. Thus, the 2019 American Heart Association guideline continue to recommend the consumption of low-fat or free-fat foods but these recommendations might need to be reconsidered in light of new information (Carson 2019).

Mechanisms of action of the effects of FD foods on cardiometabolic risk factors

The effects of FD consumption are supported by an RCT involving overweight or obese patients, which showed that the consumption of FD foods in the context of a high-dairy-fat diet induced a reduction in inflammatory biomarkers, such as the cytokine IL-6, compared with the consumption of non-FD foods (Nestel et al. 2013). In addition, the same RCT revealed that compared with the consumption of a low-dairy-fat diet, the intake of FD products resulted in significantly lower concentrations of two classes of plasmogenic lipids and increased the oxidizability of glycerophospholipids (Nestel et al. 2013). In contrast, the fermentation of dairy products produces bioactive peptides that are encrypted in milk proteins and released by the proteolytic activity of lactic acid, and they exhibit antihypertensive properties (Tamang et al. 2016) given their ability to inhibit the angiotensin enzyme (Rai et al. 2017). Previous studies have identified more than 50 peptide sequences derived from casein particularly the tripeptides isoleucine-proline-proline and valine-proline-proline, which appear to be responsible for the detected antihypertensive properties (Nagpal et al. 2011). Moreover, yogurt naturally includes lactic acid bacteria with probiotic (JAS 2014) effects; as a result, the intake of yogurt by obese and diabetic patients promotes favorable changes in the gut microbiota, which results in decreases in the glycemic response and insulin resistance (JAS 2014). Another consequence of the consumption of yogurt is an increase in the concentration of glucagon-like peptide 1 (GLP-1), which exerts an anorexigenic effect and might play a role in the potential protective effects of yogurt on obesity and diabetes (Yadav et al. 2013). Although the mechanisms explaining the beneficial effects of yogurt consumption are unknown, they are attributed to a greater bioavailability of amino acids and insulinotropic peptides and to the bacterial biosynthesis of vitamins, particularly vitamin K2, with proposed activities such as improved insulin sensitivity through the vitamin K-dependent-protein osteocalcin, anti-inflammatory properties, and lipid-lowering effects (Gille et al. 2018; Li et al. 2018). A novel strategy for the maintenance of gut health has been developed, and this strategy involves modifying the microbiome via a postbiotic treatment consisting of metabolic products secreted by live bacteria or released after bacterial lysis, modulating the microbiome to orchestrate host-microbiome interactions, and manipulating the microbiome using phage therapy (Zmora et al. 2016). The postbiotic effects might contribute to the improvement of host health by exerting specific physiological effects, even though the exact mechanisms have not been fully elucidated (Aguilar-Toalá et al. 2018). The practice of phage therapy, which involves the use of bacterial viruses (phages) or the treatment of bacterial infections, has existed for almost a century. Moreover, the combination of phages, phage-derived lytic proteins and/or antibiotics will be necessary to address growing problems, such as antibiotic-resistant infections (Lin et al. 2017).

Limitations

As is known and not unimportant, some factors, such as the number and/or type of participants, years of follow-up, and source of dietary information, identified in the results of PCSs can determine the relationship between dairy foods and cardiometabolic risk factors or/and mortality. The authors have considered the type of study used to draw the conclusions, and a summary of this information is provided in Table 1.

RCTs are needed to draw a conclusion regarding the effects of probiotics provided by fermented foods on the modification of the main specific cardiometabolic risk factors (total cholesterol, LDL-C, glycemia, body weight and hypertension) (Rondanelli et al. 2017). Based on the available findings, further studies are needed to develop specific recommendations regarding the consumption of FD products and to determine their role in the prevention of cardiometabolic diseases.

Conclusions

In conclusion, the total consumption of FD seems to be associated with a lower risk of developing stroke and CVD, whereas the consumption of yogurt appears to be associated with a lower risk of developing T2D. However, there is insufficient evidence supporting a protective relationship between FD or cheese consumption and MetS. In addition, available information regarding the association of FD, cheese and yogurt with hypertension is scarce and further evidence needs to be accumulated. Moreover, the consumption of cured cheeses by hypertensive patients should be limited due to their high sodium contents. However, the results of the described PCSs reveal that the intake of fermented foods that contain probiotics, particularly yogurt and cheese (of an undetermined type), open up new opportunities for the management of cardiometabolic risk factors.

Acknowledgments

J.C has a contract with Eurecat, Centre Tecnològic de Catalunya, Unitat de Nutrició i Salut, Reus, Spain, and A.P. has a contract with Torres Quevedo (Subprograma Estatal de

Incorporación, Plan Estatal de Investigación Científica y Técnica y de Innovación). The NFOC-Salut group is a consolidated research group of Generalitat de Catalunya, Spain (2017 SGR522).

Declaration of interest statement

No potential conflict of interest is reported by the authors.

Table 1. Levels of evidence of fermented dairy products and cardiometabolic risk factors.

Total Fermented dairy	**Level of Evidence**	**Class**
Total fermented dairy intake can reduce cardiovascular disease risk	**II**	**A**
Total fermented dairy intake can reduce stroke risk	**II**	**A**
Total fermented dairy intake has no relationship with hypertension risk	**II**	**A**
Total fermented dairy intake has a neutral relationship with metabolic syndrome risk	**II**	**A**
Cheese	**Level of Evidence**	**Class**
Cheese intake can reduce cardiovascular disease risk	**II**	**A**
Cheese intake can reduce stroke risk	**II**	**A**
Cheese intake have no relationship with metabolic syndrome risk	**II**	**B**
Cheese intake can reduce type 2 diabetes risk	**II**	**B**
Yogurt	**Level of Evidence**	**Class**
Yogurt intake have a neutral relationship with cardiovascular disease risk	**II**	**A**
Yogurt intake have a neutral relationship with stroke risk	**II**	**B**
Yogurt intake can reduce hypertension risk	**II**	**B**
Yogurt intake can reduce metabolic syndrome risk	**II**	**B**
Yogurt intake can reduce type 2 diabetes risk	**II**	**A**

IIA, systematic reviews or meta-analysis of cohort studies; IIB, individual cohort study.
Different levels of evidence-based medicine applied in this article is based from the Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)(Jeremy Howick 2009).

References

Aguilar-Toalá, J. E., Garcia-Varela, R., Garcia, H. S., Mata-Haro, V., González-Córdova, A. F., Vallejo-Cordoba, B., & Hernández-Mendoza, A. (2018). Postbiotics: An evolving term within the functional foods field. *Trends in Food Science and Technology*. https://doi.org/10.1016/j.tifs.2018.03.009

Alexander, D. D., Bylsma, L. C., Vargas, A. J., Cohen, S. S., Doucette, A., Mohamed, M., … Fryzek, J. P. (2016). Dairy consumption and CVD: a systematic review and meta-analysis. *British Journal of Nutrition*, *115*(4), 737–750. https://doi.org/10.1017/S0007114515005000

An, S.-Y., Lee, M. S., Jeon, J. Y., Ha, E. S., Kim, T. H., Yoon, J. Y., … Lee, K.-W. (2013). Beneficial Effects of Fresh and Fermented Kimchi in Prediabetic Individuals. *Annals of Nutrition and Metabolism*, *63*(1–2), 111–119. https://doi.org/10.1159/000353583

Astrup, A. (2014). Yogurt and dairy product consumption to prevent cardiometabolic diseases: Epidemiologic and experimental studies. *American Journal of Clinical Nutrition*. https://doi.org/10.3945/ajcn.113.073015

Aune, D., Norat, T., Romundstad, P., & Vatten, L. J. (2013). Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *The American Journal of Clinical Nutrition*, *98*(4), 1066–1083. https://doi.org/10.3945/ajcn.113.059030

Babio, N., Becerra-Tomás, N., Martínez-González, M. Á., Corella, D., Estruch, R., Ros, E., … PREDIMED Investigators. (2015). Consumption of Yogurt, Low-Fat Milk, and Other Low-Fat Dairy Products Is Associated with Lower Risk of Metabolic Syndrome Incidence in an Elderly Mediterranean Population. *The Journal of Nutrition*, *145*(10), 2308–2316. https://doi.org/10.3945/jn.115.214593

Borgeraas, H., Johnson, L. K., Skattebu, J., Hertel, J. K., & Hjelmesaeth, J. (2018). Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of randomized controlled trials. *Obesity Reviews*, *19*(2), 219–232. https://doi.org/10.1111/obr.12626

Britten, P., Cleveland, L. E., Koegel, K. L., Kuczynski, K. J., & Nickols-Richardson, S. M. (2012). Updated US Department of Agriculture Food Patterns Meet Goals of the 2010 Dietary Guidelines. *Journal of the Academy of Nutrition and Dietetics*. https://doi.org/10.1016/j.jand.2012.05.021

Buendia, J. R., Li, Y., Hu, F. B., Cabral, H. J., Loring Bradlee, M., Quatromoni, P. A., … Moore, L. L. (2018). Long-term yogurt consumption and risk of incident hypertension in adults. *Journal of Hypertension*. https://doi.org/10.1097/HJH.0000000000001737

Carasi, P., Racedo, S. M., Jacquot, C., Romanin, D. E., Serradell, M. A., & Urdaci, M. C. (2015). Impact of kefir derived Lactobacillus kefiri on the mucosal immune response and gut microbiota. *Journal of Immunology Research*, *2015*, 361604. https://doi.org/10.1155/2015/361604

Carson, J., Lichtenstein, A. H., & Anderson, C. (2019). Dietary Cholesterol and Cardiovascular Risk A Science Advisory From the American Heart Association. *Circulation*, *22*(2), D202. https://doi.org/10.1051/ocl/2015001

Chen, Wang, Y., Tong, X., Szeto, I. M. Y., Smit, G., Li, Z.-N., & Qin, L.-Q. (2017). Cheese consumption and risk of cardiovascular disease: a meta-analysis of prospective studies. *European Journal of Nutrition*, *56*(8), 2565–2575. https://doi.org/10.1007/s00394-016-1292-z

Companys, J., Pla-Pagà, L., Calderón-Pérez, L., Llauradó, E., Solà, R., Pedret, A., & Valls, R. M. (2020). Effects of probiotics on cardiovascular risk factors: a systematic review and meta-analyses of observational studies and randomized clinical trials. In *Advances in Nutrition*.

de Goede, J., Soedamah-Muthu, S. S., Pan, A., Gijsbers, L., & Geleijnse, J. M. (2016). Dairy Consumption and Risk of Stroke: A Systematic Review and Updated Dose-Response Meta-Analysis of Prospective Cohort Studies. *Journal of the American Heart Association*. https://doi.org/10.1161/JAHA.115.002787

Dehghan, M., Mente, A., Rangarajan, S., Sheridan, P., Mohan, V., Iqbal, R., … Yusuf, S. (2018). Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *The Lancet*. https://doi.org/10.1016/S0140-6736(18)31812-9

Drouin-Chartier, J.-P., Brassard, D., Tessier-Grenier, M., Côté, J. A., Labonté, M.-È., Desroches, S., … Lamarche, B. (2016). Systematic Review of the Association between Dairy Product Consumption and Risk of Cardiovascular-Related Clinical Outcomes. *Advances in Nutrition: An International Review Journal*, *7*(6), 1026–1040. https://doi.org/10.3945/an.115.011403

Fernández-Bodega, M. A., Mauriz, E., Gómez, A., & Martín, J. F. (2009). Proteolytic activity, mycotoxins and andrastin A in Penicillium roqueforti strains isolated from Cabrales, Valdeón and Bejes–Tresviso local varieties of blue-veined cheeses. *International Journal of Food Microbiology*, *136*(1), 18–25. https://doi.org/10.1016/j.ijfoodmicro.2009.09.014

Fernandez, M. A., & Marette, A. (2017). Potential Health Benefits of Combining Yogurt and Fruits Based on Their Probiotic and Prebiotic Properties. *Advances in Nutrition: An International Review Journal*. https://doi.org/10.3945/an.115.011114

Firouzi, S., Barakatun-Nisak, M. Y., Ismail, A., Majid, H. A., & Nor Azmi, K. (2013). Role of probiotics in modulating glucose homeostasis: evidence from animal and human studies. *International Journal of Food Sciences and Nutrition*, *64*(6), 780–786. https://doi.org/10.3109/09637486.2013.775227

Fumeron, F., Lamri, A., Abi Khalil, C., Jaziri, R., Porchay-BALDÉRELLI, I., Lantieri, O., … Tichet, J. (2011). Dairy consumption and the incidence of hyperglycemia and the metabolic syndrome: Results from a French prospective study, data from the epidemiological study on the insulin resistance syndrome (DESIR). *Diabetes Care*. https://doi.org/10.2337/dc10-1772

Gijsbers, L., Ding, E. L., Malik, V. S., de Goede, J., Geleijnse, J. M., & Soedamah-Muthu, S. S. (2016). Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. *The American Journal of Clinical Nutrition*, *103*(4), 1111–1124. https://doi.org/10.3945/ajcn.115.123216

Gille, D., Schmid, A., Walther, B., & Vergères, G. (2018). Fermented Food and Non-Communicable Chronic Diseases: A Review. *Nutrients*, *10*(4), 448. https://doi.org/10.3390/nu10040448

Godos, J., Tieri, M., Ghelfi, F., Titta, L., Marventano, S., Lafranconi, A., … Grosso, G. (2019). Dairy foods and health: an umbrella review of observational studies. *International Journal of Food Sciences and Nutrition*. https://doi.org/10.1080/09637486.2019.1625035

Guo, J., Astrup, A., Lovegrove, J. A., Gijsbers, L., Givens, D. I., & Soedamah-Muthu, S. S. (2017). Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose–response meta-analysis of prospective cohort studies. *European Journal of Epidemiology*, *32*(4), 269–287. https://doi.org/10.1007/s10654-017-0243-1

Han, J.-L., & Lin, H.-L. (2014). Intestinal microbiota and type 2 diabetes: From mechanism insights to therapeutic perspective. *World Journal of Gastroenterology*, *20*(47), 17737–17745. https://doi.org/10.3748/wjg.v20.i47.17737

Hruby, A., Ma, J., Rogers, G., Meigs, J. B., & Jacques, P. F. (2017). Associations of Dairy Intake with Incident Prediabetes or Diabetes in Middle-Aged Adults Vary by Both Dairy

Type and Glycemic Status. *The Journal of Nutrition*, *147*(9), jn253401. https://doi.org/10.3945/jn.117.253401

Hu, D., Huang, J., Wang, Y., Zhang, D., & Qu, Y. (2014). Dairy Consumption and Risk of Stroke: A Systematic Review and Updated Dose-Response Meta-Analysis of Prospective Cohort Studies. *Nutrition, Metabolism and Cardiovascular Diseases*, *24*(5), 460–469. https://doi.org/10.1016/j.numecd.2013.12.006

Huang, Y., Wu, F., Wang, X., Sui, Y., Yang, L., & Wang, J. (2013). Characterization of Lactobacillus plantarum Lp27 isolated from Tibetan kefir grains: a potential probiotic bacterium with cholesterol-lowering effects. *Journal of Dairy Science*, *96*(5), 2816–2825. https://doi.org/10.3168/jds.2012-6371

JAS, C. (2014). The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology*, *11*(8), 506–514. https://doi.org/10.1038/nrgastro.2014.66

Jeremy Howick. (2009). *Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)*. Retrieved from https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

Johansson, I., Esberg, A., Nilsson, L. M., Jansson, J. H., Wennberg, P., & Winkvist, A. (2019). Dairy product intake and cardiometabolic diseases in Northern Sweden: A 33-year prospective cohort study. *Nutrients*. https://doi.org/10.3390/nu11020284

Key, T. J., Appleby, P. N., Bradbury, K. E., Sweeting, M., Wood, A., Johansson, I., … Danesh, J. (2019). Consumption of Meat, Fish, Dairy Products, and Eggs and Risk of Ischemic Heart Disease: A Prospective Study of 7198 Incident Cases among 409 885 Participants in the Pan-European EPIC Cohort. *Circulation*. https://doi.org/10.1161/CIRCULATIONAHA.118.038813

Kim, D. H., Jeong, D., Kim, H., & Seo, K. H. (2019). Modern perspectives on the health benefits of kefir in next generation sequencing era: Improvement of the host gut microbiota. *Critical Reviews in Food Science and Nutrition*. https://doi.org/10.1080/10408398.2018.1428168

Kim, E. K., An, S.-Y., Lee, M.-S., Kim, T. H., Lee, H.-K., Hwang, W. S., … Lee, K.-W. (2011). Fermented kimchi reduces body weight and improves metabolic parameters in overweight and obese patients. *Nutrition Research*, *31*(6), 436–443. https://doi.org/10.1016/j.nutres.2011.05.011

Li, Y., Chen, J. peng, Duan, L., & Li, S. (2018). Effect of vitamin K2 on type 2 diabetes mellitus: A review. *Diabetes Research and Clinical Practice*. https://doi.org/10.1016/j.diabres.2017.11.020

Lin, D. M., Koskella, B., & Lin, H. C. (2017). Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World Journal of Gastrointestinal Pharmacology and Therapeutics*. https://doi.org/10.4292/wjgpt.v8.i3.162

Marco, M. L., Heeney, D., Binda, S., Cifelli, C. J., Cotter, P. D., Foligné, B., … Hutkins, R. (2017). Health benefits of fermented foods: microbiota and beyond. *Current Opinion in Biotechnology*, *44*, 94–102. https://doi.org/10.1016/j.copbio.2016.11.010

Mazidi, M., Mikhailidis, D. P., Sattar, N., Howard, G., Graham, I., & Banach, M. (2018). Consumption of dairy product and its association with total and cause specific mortality – A population-based cohort study and meta-analysis. *Clinical Nutrition*. https://doi.org/10.1016/j.clnu.2018.12.015

Mena-Sánchez, Becerra-Tomás, N., Babio, N., & Salas-Salvadó, J. (2018). Dairy Product Consumption in the Prevention of Metabolic Syndrome: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Advances in Nutrition (Bethesda, Md.)*. https://doi.org/10.1093/advances/nmy083

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology*. https://doi.org/10.1016/j.jclinepi.2009.06.005

Muñoz-Garach, A., Diaz-Perdigones, C., & Tinahones, F. J. (2016). Gut microbiota and type 2 diabetes mellitus. *Endocrinologia y Nutricion*. https://doi.org/10.1016/j.endonu.2016.07.008

Nagpal, R., Behare, P., Rana, R., Kumar, A., Kumar, M., Arora, S., … Yadav, H. (2011). Bioactive peptides derived from milk proteins and their health beneficial potentials: an update. *Food Funct.*, *2*(1), 18–27. https://doi.org/10.1039/C0FO00016G

Nestel, P. J., Mellett, N., Pally, S., Wong, G., Barlow, C. K., Croft, K., … Meikle, P. J. (2013). Effects of low-fat or full-fat fermented and non-fermented dairy foods on selected cardiovascular biomarkers in overweight adults. *British Journal of Nutrition*, *110*(12), 2242–2249. https://doi.org/10.1017/S0007114513001621

Nozue, M., Shimazu, T., Sasazuki, S., Charvat, H., Mori, N., Mutoh, M., … Tsugane, S. (2017). Fermented Soy Product Intake Is Inversely Associated with the Development of High Blood Pressure: The Japan Public Health Center-Based Prospective Study. *The Journal of Nutrition*, *147*(9), 1749–1756. https://doi.org/10.3945/jn.117.250282

Panahi, S., Fernandez, M. A., Marette, A., & Tremblay, A. (2017). Yogurt, diet quality and lifestyle factors. *European Journal of Clinical Nutrition*, *71*(5), 573–579. https://doi.org/10.1038/ejcn.2016.214

Parvez, S., Malik, K. A., Ah Kang, S., & Kim, H.-Y. (2006). Probiotics and their fermented food products are beneficial for health (Vol. 100, pp. 1171–1185). https://doi.org/10.1111/j.1365-2672.2006.02963.x

Petyaev, I. M., & Bashmakov, Y. K. (2012). Could cheese be the missing piece in the French paradox puzzle? *Medical Hypotheses*, *79*(6), 746–749.

https://doi.org/10.1016/j.mehy.2012.08.018
Pimenta, F. S., Luaces-Regueira, M., Ton, A. M., Campagnaro, B. P., Campos-Toimil, M., Pereira, T. M., & Vasquez, E. C. (2018). Mechanisms of Action of Kefir in Chronic Cardiovascular and Metabolic Diseases. *Cellular Physiology and Biochemistry : International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*, *48*(5), 1901–1914. https://doi.org/10.1159/000492511
Praagman, J., Dalmeijer, G. W., van der Schouw, Y. T., Soedamah-Muthu, S. S., Monique Verschuren, W. M., Bas Bueno-de-Mesquita, H., … Beulens, J. W. J. (2015). The relationship between fermented food intake and mortality risk in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort. *British Journal of Nutrition*, *113*(3), 498–506. https://doi.org/10.1017/S0007114514003766
Rai, A. K., Sanjukta, S., & Jeyaram, K. (2017). Production of angiotensin I converting enzyme inhibitory (ACE-I) peptides during milk fermentation and their role in reducing hypertension. *Critical Reviews in Food Science and Nutrition*, *57*(13), 2789–2800. https://doi.org/10.1080/10408398.2015.1068736
Ranadheera, C., Vidanarachchi, J., Rocha, R., Cruz, A., Ajlouni, S., Ranadheera, C. S., … Ajlouni, S. (2017). Probiotic Delivery through Fermentation: Dairy vs. Non-Dairy Beverages. *Fermentation*, *3*(4), 67. https://doi.org/10.3390/fermentation3040067
Rezac, S., Kok, C. R., Heermann, M., & Hutkins, R. (2018). Fermented Foods as a Dietary Source of Live Organisms. *Frontiers in Microbiology*, *9*, 1785. https://doi.org/10.3389/fmicb.2018.01785
Rondanelli, M., Faliva, M. A., Perna, S., Giacosa, A., Peroni, G., & Castellazzi, A. M. (2017). Using probiotics in clinical practice: Where are we now? A review of existing meta-analyses. *Gut Microbes*, *8*(6), 521–543. https://doi.org/10.1080/19490976.2017.1345414
Ros, E., López-Miranda, J., Picó, C., Rubio, M. Á., Babio, N., Sala-Vila, A., … FESNAD.

(2015). Consensus on fats and oils in the diet of spanish adults; position paper of the Spanish Federation of Food, nutrition and dietetics societies [Consenso sobre las grasas y aceites en la alimentación de la población española adulta; postura de la Federación. *Nutricion Hospitalaria*, *32*(2), 435–477. https://doi.org/10.3305/nh.2015.32.2.9202

Rosa, D. D., Dias, M. M. S., Grześkowiak, Ł. M., Reis, S. A., Conceição, L. L., & Peluzio, M. do C. G. (2017). Milk *kefir* : nutritional, microbiological and health benefits. *Nutrition Research Reviews*, *30*(1), 82–96. https://doi.org/10.1017/S0954422416000275

Salas-Salvadó, J., Guasch-Ferré, M., Díaz-López, A., & Babio, N. (2017). Yogurt and Diabetes: Overview of Recent Observational Studies. *The Journal of Nutrition*, *147*(7), 1452S-1461S. https://doi.org/10.3945/jn.117.248229

Seganfredo, F. B., Blume, C. A., Moehlecke, M., Giongo, A., Casagrande, D. S., Spolidoro, J. V. N., … Mottin, C. C. (2017). Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. *Obesity Reviews*, *18*(8), 832–851. https://doi.org/10.1111/obr.12541

Sluijs, I., Forouhi, N. G., Beulens, J. W. J., van der Schouw, Y. T., Agnoli, C., Arriola, L., … InterAct Consortium. (2012). The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct Study. *The American Journal of Clinical Nutrition*, *96*(2), 382–390. https://doi.org/10.3945/ajcn.111.021907

Soedamah-Muthu, S. S., & de Goede, J. (2018). Dairy Consumption and Cardiometabolic Diseases: Systematic Review and Updated Meta-Analyses of Prospective Cohort Studies. *Current Nutrition Reports*. https://doi.org/10.1007/s13668-018-0253-y

Soedamah-Muthu, S. S., Verberne, L. D. M., Ding, E. L., Engberink, M. F., & Geleijnse, J. M. (2012). Dairy consumption and incidence of hypertension: A dose-response meta-analysis of prospective cohort studies. *Hypertension*. https://doi.org/10.1161/HYPERTENSIONAHA.112.195206

Sonestedt, E., Wirfält, E., Wallström, P., Gullberg, B., Orho-Melander, M., & Hedblad, B. (2011). Dairy products and its association with incidence of cardiovascular disease: The Malmö diet and cancer cohort. *European Journal of Epidemiology*. https://doi.org/10.1007/s10654-011-9589-y

Statista. (2018). Enfermedades metabólicas: prevalencia por edad 2018 | España. Retrieved April 24, 2019, from https://es.statista.com/estadisticas/577174/prevalencia-de-las-enfermedades-metabolicas-en-espana-por-grupos-de-edad/

Tamang, J. P., Shin, D.-H., Jung, S.-J., & Chae, S.-W. (2016). Functional Properties of Microorganisms in Fermented Foods. *Frontiers in Microbiology*, *7*. https://doi.org/10.3389/fmicb.2016.00578

Tang, W. H. W., Kitai, T., & Hazen, S. L. (2017). Gut Microbiota in Cardiovascular Health and Disease. *Circulation Research*, *120*(7), 1183–1196. https://doi.org/10.1161/CIRCRESAHA.117.309715

Tang, W., Li, C., He, Z., Pan, F., Pan, S., & Wang, Y. (2018). Probiotic Properties and Cellular Antioxidant Activity of Lactobacillus plantarum MA2 Isolated from Tibetan Kefir Grains. *Probiotics and Antimicrobial Proteins*, *10*(3), 523–533. https://doi.org/10.1007/s12602-017-9349-8

Tapsell, L. C. (2015). Fermented dairy food and CVD risk. *British Journal of Nutrition*, *113*(S2), S131–S135. https://doi.org/10.1017/S0007114514002359

Thushara, R. M., Gangadaran, S., Solati, Z., & Moghadasian, M. H. (2016). Cardiovascular benefits of probiotics: a review of experimental and clinical studies. *Food & Function*, *7*(2), 632–642. https://doi.org/10.1039/c5fo01190f

Toscano, M., De Grandi, R., Pastorelli, L., Vecchi, M., & Drago, L. (2017). A consumer's guide for probiotics: 10 golden rules for a correct use. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association* *for the Study of the Liver*, *49*(11), 1177–1184. https://doi.org/10.1016/j.dld.2017.07.011

Tremblay, A., & Panahi, S. (2017). Yogurt Consumption as a Signature of a Healthy Diet and Lifestyle. *The Journal of Nutrition*, *147*(7), 1476S-1480S. https://doi.org/10.3945/jn.116.245522

Wang, Z., Cui, Y., Liu, P., Zhao, Y., Wang, L., Liu, Y., & Xie, J. (2017). Small Peptides Isolated from Enzymatic Hydrolyzate of Fermented Soybean Meal Promote Endothelium-Independent Vasorelaxation and ACE Inhibition. *Journal of Agricultural and Food Chemistry*, *65*(50), 10844–10850. https://doi.org/10.1021/acs.jafc.7b05026

Wu, L., & Sun, D. (2017). Consumption of yogurt and the incident risk of cardiovascular disease: A meta-analysis of nine cohort studies. *Nutrients*. https://doi.org/10.3390/nu9030315

Xiang, H., Sun-Waterhouse, D., Waterhouse, G. I. N., Cui, C., & Ruan, Z. (2019). Fermentation-enabled wellness foods: A fresh perspective. *Food Science and Human Wellness*. https://doi.org/10.1016/j.fshw.2019.08.003

Yadav, H., Lee, J.-H., Lloyd, J., Walter, P., & Rane, S. G. (2013). Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *The Journal of Biological Chemistry*, *288*(35), 25088–25097. https://doi.org/10.1074/jbc.M113.452516

Yoo, J. Y., & Kim, S. S. (2016). Probiotics and Prebiotics: Present Status and Future Perspectives on Metabolic Disorders. *Nutrients*, *8*(3), 173. https://doi.org/10.3390/nu8030173

Zmora, N., Zeevi, D., Korem, T., Segal, E., & Elinav, E. (2016). Taking it Personally: Personalized Utilization of the Human Microbiome in Health and Disease. *Cell Host and Microbe*. https://doi.org/10.1016/j.chom.2015.12.016